

MedNous

Managing European Medical Innovation

Review Article **Value-based drug pricing gains favour**

Page 5

Technology Transfer **The US National Cancer Institute at work**

By Michael Salgaller and Michele Newton

Page 8

Emerging Trends **Europe's pharma groups change product mix**

By Robin Davison

Page 16

Licensing and Collaboration Briefs

Page 4

Plus

Commentary

Building capacity in Europe for advanced therapies

By Yasmin de Faria Krim

Page 25

Regulatory News

Scott Gottlieb to leave FDA
Breast cancer approval for Tecentriq

Page 11

Finance

Size of European funding rounds increases

Page 18

Cell and Gene Therapy

Patient with HIV in remission

Page 29

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See page 2 ▶

NCI and industry: Michael Salgaller and Michele Newton

Moving innovations from the lab to patients

In the autumn of 2017, staff at the US National Cancer Institute's Technology Transfer Center welcomed an unexpected guest: a cancer patient who was supposed to have died due to his disease months earlier. He had recently been treated with a monoclonal antibody that blocks a protein on the surface of tumour cells enabling the immune system to fight cancer. The treatment, avelumab, had stopped this highly lethal form of skin cancer, Merkel cell carcinoma, from progressing.

Avelumab, known commercially as Bavencio, is a checkpoint antibody that was given an accelerated approval by the US Food and Drug Administration on 23 March 2017. At the time, it was the first checkpoint antibody to receive FDA approval for this disease¹. Since then, pembrolizumab, known commercially as Keytruda, has also been authorised to treat Merkel cell carcinoma.

A pioneering therapy, Bavencio received early interest from the Technology Transfer Center which worked closely with NCI researchers to facilitate a collaboration with the developer EMD Serono, the biopharmaceutical division of Merck KGaA.

For decades, NCI collaborations such as this one have led to FDA approvals of many new cancer treatments. Still, face-to-face interactions with cancer patients whose lives were extended because of new cancer therapies was something special that the technology transfer team was able to experience. For a group used to working primarily behind the scenes, it was a gratifying moment that illustrated the consequential role of technology transfer for patients and the public at large.

The NCI is one of 27 Institutes and Centers comprising the National Institutes of Health, the largest biomedical research agency in the world. Its parent agency, the US Department of Health and Human Services, was recently ranked the top government innovator by Reuters². Within the NCI, the Technology Transfer Center facilitates and manages transactional, co-development and licensing partnerships with companies in the life science, device, diagnostic and digital health sectors, as well as with universities, non-profit organisations and other government laboratories. The Center also works closely with intramural researchers to manage the intellectual property arising from their discoveries. The NIH is prohibited by internal policy from engaging in commercial activities directly related to the commercialisation of its own inventions. Thus government-industry partnerships are required to co-develop or out-license such technologies.

The NCI Center for Cancer Research is the largest division of the NCI intramural research programme and comprises nearly 250 basic and clinical research groups located on two campuses outside of Washington DC. The Center for Cancer Research is also home to some of the top cancer researchers in the world, including the 2018 and 2019 winners of the annual Szent-Györgyi Prize for Progress in Cancer Research. Douglas R. Lowy and John T. Schiller of the National

Cancer Institute were recognised in 2018 for their role in the development of vaccines for human papilloma virus (HPV). Drs Lowy and Shiller developed the first Food and Drug Administration-approved vaccines specifically targeting cancer. Dr Steven Rosenberg was announced as the winner of the prize for 2019 for his "pioneering role in the development of adoptive immunotherapy to treat cancer^{3, 4}."

The mission of the Center for Cancer Research is "to improve the lives of cancer patients by solving important, challenging and neglected problems in cancer research and patient care." Thus, since it is not driven by profits, NCI's patented inventions need commercial entities to move potential treatments from bench and bedside to the market – a considerable gap. To help bridge that gap, the Technology Transfer Center takes a proactive approach to match NCI technologies with potential partners that have an aligned technology and a strategic interest in development. Partnerships also originate from companies where they bring in a cancer technology to co-develop with the NCI.

The avelumab collaboration

Avelumab was discovered by scientists in Merck KGaA/EMD Serono's labs. In November 2014, Merck KGaA and Pfizer announced a global strategic alliance to co-develop and co-commercialise avelumab in multiple types of cancer including metastatic Merkel cell carcinoma, a lethal skin cancer. At the time of the alliance announcement, avelumab was in a Phase 2 clinical study of Merkel cell carcinoma where it had generated promising data⁵. As described earlier, avelumab is a checkpoint antibody. It specifically inhibits the programmed death-ligand 1 (PD-L1) on the cell surface of tumour cells, thus preventing the inactivation of immune cells and keeping them available for tumour destruction.

Through a Cooperative Research and Development Agreement negotiated by the NCI Technology Transfer Center, EMD Serono partnered with NCI to develop avelumab. Studies of avelumab aligned with research already being conducted by Jeffrey Schlom, chief of the Institute's Laboratory of Tumor Immunology and Biology, and James Gulley, director of the Institute's medical oncology service. Drs Schlom and Gulley are internationally recognised experts in cancer immunotherapy, and Dr Gulley has conducted a variety of NCI clinical trials. These innovative, investigator-initiated studies involve the use of cancer immunotherapy to (a) initiate immune responses, (b) expand immune responses and/or (c) allow the immune responses to be effective within the tumour microenvironment⁶.

NCI began studies of avelumab while the drug was in the earliest stages of development. Successful preclinical studies provided the foundational support for moving forward with clinical investigations for multiple indications. Successful Phase 1 clinical studies conducted at the NIH Clinical Center led to studies with multiple expansion cohorts. One

of these cohorts focused on urothelial carcinoma. Also, a Phase 2 trial in metastatic Merkel cell carcinoma was conducted that would, for the first time, look at whether avelumab would benefit patients with this disease. NCI also conducted important studies necessary for avelumab's regulatory approval. Amazingly, in less than four years from the first NCI studies, avelumab received its accelerated FDA approval for Merkel cell carcinoma, followed shortly thereafter by FDA approval for previously treated, locally advanced or metastatic urothelial carcinoma.

The approval for Merkel cell carcinoma was based on data from a single-arm trial of 88 patients with metastatic disease who had previously been treated with at least one prior chemotherapy regime. The trial measured the percentage of patients who experienced a complete or partial shrinkage of their tumours and, for patients with a response, the duration of that response, or the length of time the tumour was controlled. Thirty-three percent of patients in the trial experienced complete or partial tumour shrinkage. The response lasted for more than six months in 86% of responding patients and more than 12 months in 45% of responding patients. Up until this approval, the standard of care for metastatic Merkel cell carcinoma was chemotherapy. Although response rates to chemotherapy have been high, more than 50% of patients receiving these treatments had their cancers return after three months⁷.

The range of collaborations at NCI

The Technology Transfer Center facilitates a wide assortment of collaborations between the Institute and external stakeholders, including companies, entrepreneurs and investors. The staff of the Center is comprised of professionals with advanced technical degrees, law degrees and masters of business administration. They advise and facilitate a wide assortment of technology development and commercialisation agreements. These agreements provide a scientific, legal and financial framework to exchange research materials, enter complex collaboration agreements and transfer invention rights via licences.

These activities are crucial because the NIH, of which NCI is a part, cannot directly commercialise its inventions or create commercial entities to do so. As a result, although hundreds of medical innovations arise from the NIH each year, they risk not progressing beyond the lab. Technologies must be transferred – hence the term technology transfer – to an entity that can advance them along the product development continuum, obtain regulatory approval to market, and make them available to the public.

Industry will not commercialise early-stage inventions because many of them are too risky to bring to the market. Unproven technology requires capital, potentially more than €1 billion, and takes time to develop. NIH policy aligns with this reality. For technologies originating from NIH researchers, companies (and other buy-side stakeholders such as entrepreneurs and investors) negotiate exclusive IP rights for certain indications and geographies. The NIH offers unique, sound business terms, such as taking no equity upon licence execution. For public companies, maintaining a percentage ownership is highly attractive to shareholders and the public markets. For private companies, maintaining percentage ownership is highly attractive to

current as well as potential investors.

Companies also co-develop medical products, and the associated IP, with NIH researchers using a wide range of collaborative agreements. A needs assessment is done to determine which agreement best fits the strategic goals of each side. Any IP that a company brings into the partnership remains theirs. When new IP is created, it is jointly owned. However, the NIH cannot advance the IP towards commercialisation. Therefore, under a specific collaborative agreement known as the Cooperative Research and Development Agreement, the company partner receives an option to an exclusive licence. There is no risk to the company partner that the NIH might create a spin out ("NewCo") and compete with it for the newly created IP. Thus, companies have the opportunity to enhance their developmental pipelines.

Whether the straight licence of an NIH asset or something jointly created, both sides negotiate milestone and royalty payments that go right back into the NIH's research budget. Monies are shared among all 27 Institutes and Centers

Each year, the NIH collaborates with hundreds of industry partners around the world, from start-ups to global pharmas. It licenses out dozens of inventions and files dozens of patents. All of these essential activities require the input of NIH's highly skilled technology transfer professionals.

In summary, technology transfer activities increase the ability of the NIH to impact and improve public health – effectively meeting its mission. Importantly and additionally, technology transfer activities with industry enhance economic well-being and ensure a continued high return on the public investment in research, helping the NIH meet this lesser known, yet undoubtedly valuable part of its mission. In these ways – whether helping treat a disease impacting millions of people, or a rare disorder afflicting the few – the NIH continues to stand, as it has for decades, as a beacon of hope to people around the world.

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